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Determinants of High-Risk HPV Seroprevalence and DNA Prevalence in Mid-Adult Women

Pat Sadate-Ngatchou, PhD, MPH[*], **Joseph J. Carter, PhD**[†], **Stephen E. Hawes, PhD**[‡], **Qinghua Feng, PhD**[§], **Taylor Lasof**[¶], **Joshua E. Stern, MS**[‖], **Tsung-chieh (Jane) Fu, PhD**[‡], **Denise A. Galloway, PhD**[†,**], **Laura A. Koutsky, PhD**[‡], and **Rachel L. Winer, PhD**[‡]

[*]Clinton Health Access Initiative, Yaounde, Cameroon

[†]Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[‡]Department of Epidemiology, University of Washington, Seattle, WA, USA

[§]FIDALAB, Seattle, WA, USA

[¶]University of California San Diego, La Jolla, CA, USA

[‖]Department of Global Health, University of Washington, Seattle, WA, USA

[**]Department of Microbiology, University of Washington, Seattle, WA, USA

Abstract

Background—The epidemiology of hrHPV infections in mid-adult women is not well understood.

Methods—We conducted a cross-sectional analysis of 379 30–50 year old females. Vaginal samples were tested for type-specific HPV DNA by PCR. Sera were tested for type-specific HPV antibodies by Luminex-based assay. Assays included 13 hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59/68). Self-reported health and sexual history were ascertained. Risk factors for seropositivity and DNA positivity to hrHPV were assessed in separate Poisson regression models.

Results—The mean (standard deviation) age of participants was 38.7 (6.1) years, and the median lifetime number of male sex partners was 7. About two-thirds (68.1%) were seropositive for any hrHPV, 15.0% were DNA positive, and 70.7% were seropositive or DNA positive. In multivariate analyses, women who were married/living with a partner were less likely to be seropositive than single/separated women (adjusted prevalence ratio [aPR]=0.86, 95%CI:0.75–0.98). Compared to never hormonal contraceptive users, current (aPR=1.53,95%CI:1.01–2.29) or former (aPR=1.64,95%CI:1.10–2.45) users were more likely to be seropositive. Women with a lifetime number of sex partners ≥12 were more likely to be seropositive compared to those with 0–4 partners (aPR=1.29,95%CI:1.06–1.56). Similar associations were seen with DNA positivity. In addition, there was a positive association between current smoking and hrHPV DNA (aPR versus never smokers=2.51, 95%CI:1.40–4.49).

Corresponding author: Rachel L. Winer, PhD, University of Washington HPV Research Group, Box 359933, 325 9th Ave., Seattle, WA 98104, USA, Tel: +1 206-616-5081, Fax: +1 206-616-9788, rlw@uw.edu.

Conclusions—71% of mid-adult women had evidence of current or prior hrHPV infection. Measures of probable increased exposure to HPV infection were associated with both seropositivity and DNA positivity to hrHPV, whereas current smoking was positively associated with hrHPV DNA only.

Keywords

HPV; human papilloma virus; women; prevalence; risk factors

INTRODUCTION

Human papillomavirus (HPV) infections are common and sexually transmitted.[1] While 90% of infections become undetectable within 12–18 months, a minority persist.[2] Persistent infection with high-risk (hr) HPV types is necessary for the development of cervical cancer.[2] In the U.S., prophylactic vaccines targeting the hrHPV types linked to 70% of cervical cancers (HPV-16 and HPV-18) have been widely available since 2006.[3] In 2014, the U.S. FDA approved a vaccine targeting an additional 5 hr types (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58) that increase coverage against cervical cancer to 90%.[4] Prophylactic HPV vaccines are licensed for females and males aged 9–26 years, with the recommended ages of 11–12 years designed to target adolescents prior to sexual debut.[3, 4] Because current vaccines are prophylactic and not therapeutic, the potential benefit for women older than 26 years is undefined. Additional epidemiologic data on hrHPV infections in mid-adult women – including data on the proportion of women with evidence of current or prior infection – can help to inform vaccine recommendations in this age group.

hrHPV DNA assays measure presence of current infection only. Despite limitations of serology (not all women mount a detectable antibody response following natural infection,[5] antibody levels may wane over time,[6] and assay sensitivity is limited[7]), detection of hrHPV antibodies contributes useful information on prior and cumulative exposure to hrHPV infection. To better understand the epidemiology of hrHPV infections in mid-adult women, we evaluated both DNA prevalence and seroprevalence for 13 hrHPV types in 30 to 50 year old women in Seattle, Washington. In addition, we determined risk factors associated with seropositivity and DNA positivity.

METHODS

To assess prevalence and determinants of hrHPV DNA and antibodies in mid-adult women, we performed a cross-sectional analysis using baseline data from a 6-month longitudinal study of HPV infections conducted from 2011–2012.[8] Recruitment, screening, and enrollment procedures for the study were described previously.[8] Briefly, study participants were recruited via flyers, advertisements and letters distributed to students, faculty and staff at the University of Washington (UW). Women who were aged 30–50 years and affiliated with the UW were eligible to enroll. Women who were currently pregnant, had undergone hysterectomy, or had any serious medical conditions that would preclude study participation were not eligible. The study protocol was reviewed and approved by the UW Institutional Review Board, and all subjects provided written informed consent.

Enrollment visits occurred at the on-campus UW Hall Health Primary Care Center. Procedures have been described in detail previously.[8] Briefly, the enrollment visit included a face-to-face interview on cervical cancer screening and HPV vaccination history; a self-administered online survey on socio-demographics, health history, contraceptive use, smoking habits, and sexual behaviors; a self-collected vaginal swab sample for HPV DNA testing; and a blood draw for HPV antibody testing.

Genomic DNA was extracted from vaginal specimens and used for HPV genotyping. Vaginal samples were digested with 20 μg/mL protease K at 37°C for one hour, and DNA isolated from 200 μL of the digested sample using QIAmp DNA blood mini column according to the manufacturer's protocol (Qiagen, Cat. No.51104, Valencia, CA). DNA samples were then directly genotyped by polymerase chain reaction (PCR) for detection of 37 alpha genus types using the Roche Linear Array HPV genotyping test (Roche Molecular Systems, Inc., Alameda, CA), which uses a β-globin control. For this analysis, we included 13 hrHPV types (16/18/31/33/35/39/45/51/52/56/58/59/68[9]) for which serology data were also available.

Antibody testing was performed using a Luminex-based assay described in detail previously.[10, 11] Briefly, HPV 16/18/31/33/35/39/45/51/52/56/58/59/68 L1 proteins and BKPyV VP1 proteins (a positive control) were expressed as glucathione S-transferase (GST)-fusion proteins. Human sera were tested at a final dilution of 1:100. For each sample, the median fluorescent intensity (MFI) for GST-tag (empty vector control) was subtracted from the MFI of the other antigens. The cut point for determining HPV-16 antibody positivity, MFI=1,000, was selected by visual inspection of the MFI distribution and informed by previous studies using this technique.[12] Cut points for other types were adjusted if their distribution was significantly different than HPV-16 values. We selected the following cut points: 2,000 for HPV-35; 1,000 for HPV-18/31/51/52/56/58/59; and 500 for HPV-33/39/45/68. Serologic controls included the HPV-16 international standard (10 U/ml) (National Institute for Biological Standards and Controls) and a serum being evaluated by the World Health Organization as a potential HPV-18 standard. The HPV-16 standard was consistently positive for HPV-16 (average[a]MFI=2458; 95%CI:2178–2738). The HPV-18 control was positive in 7 of 8 tests (aMFI=1193; 95%CI:994–1441), and also consistently positive for HPV-45 (aMFI=15207; 95%CI:12631–17784), indicating potential cross-reactivity between HPV-18 and HPV-45. For HPV-16, the cut point of MFI=1,000 was calculated to be the equivalent of 6.3 international HPV-16 units/mL. Reliability was assessed by re-testing a random 10% of samples. The pooled type-specific concordance between the initial test and the re-test was 90%, and the pooled type-specific Cohen's kappa statistic was 0.58 (moderate).

Subjects who self-reported a history of prophylactic HPV vaccination were excluded from all analyses. To examine socio-demographic and health and behavioral risk factors associated with 1) seroprevalence and 2) DNA prevalence to any of the 13 hrHPV types tested, we determined unadjusted prevalence ratios (PRs) and 95% confidence intervals (CI) using Poisson regression for each of the following possible determinants: age, race, marital status, number of pregnancies, cigarette usage, hormonal contraceptive use, lifetime number

of male sex partners, age at sexual debut, male sex partners within the past 6 months, history of non-HPV related STDs, history of an abnormal Pap test, and history of genital warts.

In separate analyses restricted to seropositive women, each risk factor was evaluated to determine whether it was associated with seropositivity to multiple hrHPV types vs a single hrHPV type. For all models, risk factors statistically significant ($p<0.10$) in univariate analyses were entered into a final multivariate Poisson regression model.

RESULTS

A total of 409 women were enrolled. Thirty (7%) were excluded from analyses due to self-reported history of HPV vaccination. Demographic, health and sexual behavior characteristics of the remaining 379 women are described in Table 1. Their mean age was 38.7 (standard deviation 6.1) years and their median lifetime number of male sex partners was 7 (interquartile range 3–15).

All enrollment sera were positive for BKV, and all enrollment vaginal samples were positive for β-globin. Overall, 68.1% of women were seropositive and 15.0% were DNA positive for any of 13 hrHPV types, and 70.7% were positive by either serology or PCR. (Table 2) In addition, 45.1% of all women tested positive for antibodies to multiple hrHPV types, whereas only 4.5% were DNA positive to multiple hrHPV types. Considering HPV types included in prophylactic vaccines, 50.7% of women were either seropositive or DNA positive to any of the 7 hrHPV types included in the 9-valent vaccine (HPV 16/18/31/33/45/52/58), and 31.9% were seropositive or DNA positive to either of the 2 hrHPV types included in the bivalent and quadrivalent vaccines (HPV 16 and 18). Furthermore, 10.0% of women were seropositive or DNA positive to both HPV-16 and HPV-18. The most commonly detected HPV serotypes were HPV-59 (26.1%), HPV-31 (25.9%), HPV-51 (25.6%), and HPV-16 (25.1%), whereas HPV-51 (3.4%) and HPV-16 (3.4%) were the types most commonly detected by PCR.

On the infection-level, a total of 904 type-specific hrHPV infections were detected by either serology or PCR. These included 825 type-specific infections detected by serology only, 46 detected by PCR only, and 33 jointly detected by both assays. Whereas only 3.9% (33 of 858) of type-specific seropositives were jointly DNA positive for the same HPV type, 41.8% (33 of 79) of type-specific DNA positives were jointly seropositive for the same HPV type.

In multivariate analyses, women who were married or living with a partner were less likely to be hrHPV seropositive compared to single or separated women (adjusted prevalence ratio [aPR]=0.86, 95% CI:0.75–0.98). (Table 3) In addition, compared to women who had never used hormonal contraceptives, those who were current (aPR=1.53, 95% CI:1.01–2.29) or former (aPR=1.64, 95% CI:1.10–2.45) users were more likely to be seropositive. Women with lifetime numbers of male sex partners equal to or more than 12 were more likely to be seropositive compared to those with 0–4 partners (aPR=1.29, 95% CI:1.06–1.56). Compared to women reporting their race as white, those reporting any other race (excluding Asian) or more than one race were borderline statistically significantly more likely to be seropositive (aPR=1.18, 95% CI:0.99–1.41).

Moreover, we evaluated risk factors associated with seropositivity to multiple hrHPV types versus a single hrHPV type. (Table 4) In multivariate analysis, compared to women who had never been pregnant, those who reported ≥4 pregnancies had a borderline statistically significant increased likelihood of seropositivity to multiple hrHPV types versus a single hrHPV type (aPR=1.24, 95% CI:0.98–1.57). Likewise, women who reported a lifetime number of ≥12 male sex partners (aPR=1.33, 95% CI:0.98–1.80) were borderline statistically significantly more likely to be seropositive to multiple hrHPV types compared to women who reported 0–4 partners (Table 4).

In multivariate analyses, women who were married or living with a partner were less likely to be DNA-positive to any hrHPV type when compared to single or separated women (aPR=0.50, 95% CI:0.30–0.82). (Table 5) Compared to never smokers, current smokers were more likely to be hrHPV DNA positive (aPR=2.51, 95% CI:1.40–4.49). Moreover, compared to women with a lifetime number of 0–4 male sex partners, those with ≥12 (aPR=2.23, 95%CI:0.99–5.06) were borderline statistically significantly more likely to be hrHPV DNA positive.

DISCUSSION

To assess both current genital infection and cumulative exposure to hrHPV in a population of mid-adult women 30 to 50 years of age, we evaluated both DNA prevalence in vaginal swabs and seroprevalence. While numerous studies have reported on hrHPV DNA prevalence for multiple genotypes, most hrHPV seroprevalence studies have focused on HPV-16 and HPV-18 only. A handful of studies have reported on 5–10 additional hr types,[13–18] but to our knowledge, this prevalence report includes the largest number of hrHPV serotypes to date in a population of women. We targeted the 13 hrHPV types most strongly associated with cervical carcinogenesis.[9] (These types are included in commercially-available HPV DNA assays for routine cervical cancer screening [some commercially available assays also include HPV-66, a possibly carcinogenic type that we did not evaluate by serology].) Fifteen percent of the women in our cohort had detectable hrHPV DNA in self-collected vaginal samples (comparable to hrHPV prevalence in cervical samples from similarly aged women undergoing routine cervical cancer screening[19]), and an additional 56% had evidence of prior hrHPV infection through positive serology. While comparisons across populations are complicated by differences in populations studied and serology assays used (including number of hrHPV types targeted), we compared our seroprevalence estimates for individual types HPV-16 and HPV-18 to U.S. national data among similar-aged women,[20] and noted that our estimates were higher (25% versus 17%–22% for HPV-16 and 14% versus 7%–10% for HPV-18).

The women included in our analysis self-reported no history of HPV vaccination. Thirty-two percent demonstrated evidence of natural infection with HPV-16 and/or HPV-18 (through positive DNA and/or serology), but only 10% showed evidence of current or prior infection with both of these vaccine types. Given that most women were naïve to one of these hr types (and the availability of a 9-valent vaccine against 5 additional hrHPV types), our results suggest that prophylactic HPV vaccination could be beneficial for subgroups of mid-adult women at risk for exposure to new hrHPV infections.

On the infection level, almost all (96%) seropositives were concurrently DNA negative for the same type. These data are in agreement with previous reports in varying populations of women,[16, 21] and reflect the transient and sporadic nature of hrHPV DNA detection. As noted by others,[21] a portion of the seropositivity detected in women without current evidence of genital DNA may also reflect infection at non-genital sites.

The most commonly detected hrHPV serotypes in our cohort included HPV-59, HPV-31, HPV-51, and HPV-16. Two of these types, HPV-51 and HPV-16, were also among the most prevalent DNA types, whereas HPV-59 and HPV-31 were not, suggesting that these latter two types may clear (or become undetectable) faster or more frequently than HPV-16 and HPV-51.

Consistent with reports in various populations of women, 58% of DNA positives were concurrently seronegative for the same type.[16, 21–23] These cases likely reflect a combination of sample mistiming (given that seroconversion occurs a median of 12 months after initial infection,[6] sampling early in the course of infection may not yield detectable antibody), failure to seroconvert,[5] waning antibody,[6] and limitations in assay sensitivity.[7]

The likelihood of seroconversion after natural infection is not well-understood, but likely depends on a combination of host and viral factors. As reported by others, hrHPV seropositivity was positively associated with markers of increased sexual activity (and thus increased cumulative viral exposure), including single or separated marital status and increased lifetime number of sex partners.[14, 18, 21, 23–26] Though the associations were not always statistically significant (due to the smaller number of outcomes), similar and even more pronounced associations were seen with hrHPV DNA positivity. This was not unexpected, given that the majority of prevalent hrHPV infections detected in this age group likely represented persistent infection.

Associations of hrHPV seropositivity with both former and current hormonal contraceptive use are consistent with some[21, 23, 25] but not all[24, 27] previous reports, and remained significant after adjusting for sexual history variables. Hormonal contraceptive use may modulate antibody production through direct modulation of the local mucosal immune response, as suggested by data demonstrating higher cervical immunoglobulin levels in oral contraceptive users versus non-users.[28] The magnitude of association of hormonal contraception with hrHPV DNA positivity was similar, though not statistically significant.

Nearly half of women showed evidence of current or prior infection with more than one hrHPV type. Multiple-type seropositivity could be due partially to assay cross-reactivity. Our analyses of HPV-16 and HPV-18 standards showed cross-reactivity between HPV-18 and HPV-45, but no cross-reactivity associated with HPV-16. Seropositivity to multiple hrHPV types versus a single hrHPV type was positively associated with increasing lifetime number of male sex partners and increasing number of pregnancies. The latter could reflect hormonal mechanisms similar to those postulated for the association between hormonal contraceptive use and increased seropositivity.

Whereas smoking status was unassociated with hrHPV seropositivity, current smoking was positively associated with hrHPV DNA detection. The literature on associations of smoking

with HPV serology and/or HPV DNA have been mixed.[1, 16, 18, 21, 24, 25] However, it is plausible that cigarette smoking may decrease antibody response to infection by suppressing immunity, contributing to increased likelihood of persistent infection.[16] This could explain the observed association between smoking and hrHPV DNA detection in the absence of an association between smoking and hrHPV seropositivity.

Limitations to our study should be noted. While multiplex GST-L1 assays are amenable to HPV seroepidemiology studies (due to the ability to simultaneously detect antibodies to multiple type-specific HPV antigens in a high-throughput, low-cost manner), they may be slightly less accurate than virus-like particle-based enzyme-linked immunosorbent assays.[29] The analysis was cross-sectional, and thus captured DNA and serostatus at only one point in time. Though the data are drawn from a longitudinal study, serostatus was measured at baseline only, and thus analyses aimed at understanding serostatus over time or predictors of seroconversion in mid-adult women were not possible. Moreover, we did not have sufficient power to stratify our seropositivity risk factor analyses by hrHPV DNA status, and were thus unable to specifically identify risk factors for seropositivity in mid-adult women with current evidence of genital infection. Finally, our study population included mostly well-educated women who were all affiliated with the University of Washington, and thus results may not generalize to other populations of mid-adult women with different risk profiles. Notably, however, the median lifetime number of male sex partners reported by the women in our cohort (7 partners) was higher than that reported in a population-based sample of 25 to 44 year old women participating in the 2006–2008 National Survey of Family Growth (3.6 partners).[30]

In conclusion, 71% of the mid-adult women in our study showed evidence of current or prior infection with any of 13 hrHPV types, and in the majority of cases, evidence of prior infection was detected in the absence of current infection. The majority of participants were naïve to at least one of the two hrHPV types included in all prophylactic vaccines (HPV-16 and HPV-18), indicating potential benefit of vaccination for subgroups of high-risk women. Measures of probable increased exposure to HPV infection (single or separated marital status, increased lifetime number of sex partners and hormonal contraceptive use) were associated with both seropositivity and DNA positivity to hrHPV, whereas current smoking was positively associated with hrHPV DNA positivity only. Larger, longitudinal studies are needed to examine risk factors for seroconversion in mid-adult women with evidence of hrHPV DNA.

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Table 1

Demographic, health and sexual behavior characteristics of 30–50 year old women in Seattle, Washington who were tested for high-risk HPV DNA in self-collected vaginal swabs and high-risk HPV DNA antibodies (N=379).

Variable	n	(%)
Age (years)		
30–34	138	(36.4)
35–39	91	(24.0)
40–44	73	(19.3)
45–50	77	(20.3)
Race		
White	299	(78.9)
Asian	42	(11.1)
Other*	38	(10.0)
Education		
Some college or less	64	(16.9)
College bachelor's degree	137	(36.2)
College master's or doctoral degree	178	(47.0)
Marital status		
Single or separated	147	(38.8)
Married or living with partner	231	(61.0)
Missing	1	(0.3)
Smoking status		
Never smoker	278	(73.4)
Former smoker	81	(21.4)
Current smoker	19	(5.0)
Missing	1	(0.3)
Number of pregnancies		
0	149	(39.3)
1–3	184	(48.6)
≥ 4	46	(12.1)
Hormonal contraceptive use		
Never	40	(10.6)
Former	212	(55.9)
Current	127	(33.5)
Age at sexual debut (years)		
≤15	65	(17.2)
16–19	178	(47.0)
≥ 20	120	(31.7)

Variable	n	(%)
Missing	16	(4.2)
Lifetime number of male sex partners[†]		
0–4	130	(34.3)
5–11	119	(31.4)
12+	126	(33.3)
Missing	4	(1.1)
Male sex partners in past 6 months		
No partners	82	(21.6)
Non-new partners only	206	(54.4)
≥1 new partner	84	(22.2)
Missing	7	(1.9)
History of non-HPV-related STDs[‡]		
Yes	76	(20.1)
No	301	(79.4)
Missing	2	(0.5)
History of abnormal Pap test		
Yes	158	(41.7)
No	221	(58.3)
History of genital warts		
Yes	42	(11.1)
No	337	(88.9)

[*] Other race included: African American, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, women reporting more than one race, and women reporting “other” as race.

[†] This category represents approximate tertiles.

[‡] Non-HPV-related STDs included: chlamydia, herpes, gonorrhea, HIV, and syphilis.

Table 2

Seroprevalence and DNA Prevalence by HPV type in mid-adult women (N=379).

	Antibody positive		DNA positive		Antibody or DNA positive	
	n	(%)	n	(%)	n	(%)
HPV-16	95	(25.1)	13	(3.4)	103	(27.2)
HPV-18	54	(14.2)	5	(1.3)	56	(14.8)
HPV-31	98	(25.9)	5	(1.3)	100	(26.4)
HPV-33	43	(11.3)	1	(0.3)	44	(11.6)
HPV-35	52	(13.7)	2	(0.5)	54	(14.2)
HPV-39	78	(20.6)	7	(1.8)	83	(21.9)
HPV-45	33	(8.7)	3	(0.8)	34	(9.0)
HPV-51	97	(25.6)	13	(3.4)	103	(27.2)
HPV-52	23	(6.1)	8	(2.1)	31	(8.2)
HPV-56	82	(21.6)	8	(2.1)	86	(22.7)
HPV-58	67	(17.7)	6	(1.6)	71	(18.7)
HPV-59	99	(26.1)	5	(1.3)	100	(26.4)
HPV-68	37	(9.8)	3	(0.8)	39	(10.3)
Any high-risk HPV	258	(68.1)	57	(15.0)	268	(70.7)
Multiple high-risk HPV	171	(45.1)	17	(4.5)	176	(46.4)
Any high-risk HPV in the 9-valent vaccine*	183	(48.3)	39	(10.3)	192	(50.7)
HPV-16 or HPV-18	113	(29.8)	18	(4.7)	121	(31.9)
HPV-16 and HPV-18	36	(9.5)	0	(0.0)	38	(10.0)

*HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, and/or HPV-58

Table 3

Analysis of risk factors associated with seropositivity to any high-risk HPV type in mid-adult women (N=379).

		hrHPV Antibody				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**AB+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Age (years)						
30–34	138	98 (71.1)	1.00	ref	1.00	ref
35–39	91	65 (71.4)	1.01	0.85 – 1.19	0.97	0.82 – 1.15
40–44	73	50 (68.5)	0.96	0.80 – 1.16	0.91	0.75 – 1.10
45–50	77	45 (58.4)	0.82	0.66 – 1.02	0.85	0.69 – 1.06
Race						
White	299	201 (67.2)	1.00	ref	1.00	Ref
Asian	42	26 (61.9)	0.92	0.72 – 1.18	1.07	0.83 – 1.38
Other†	38	31 (81.6)	1.21	1.02 – 1.44	1.18	0.99 – 1.41
Age at Sexual debut (years)						
≤15	65	48 (73.8)	1.00	ref		
16–19	178	121 (68.0)	0.92	0.77 – 1.10		
≥20	120	79 (65.8)	0.89	0.73 – 1.08		
Marital status						
Single or separated	147	112 (76.2)	1.00	ref	1.00	ref
Married or living with a partner	231	145 (62.8)	0.82	0.72 – 0.94	0.86	0.75 – 0.98
Number of pregnancies						
0	149	107 (71.8)	1.00	ref		
1–3	184	123 (66.9)	0.93	0.81 – 1.07		
≥4	46	28 (60.9)	0.85	0.66 – 1.09		
History of abnormal Pap test	158	120 (76.0)	1.22	1.06 – 1.39	1.10	0.96 – 1.27
History of genital warts	42	30 (71.4)	1.06	0.86 – 1.30		
History of non-HPV-related STD‡	76	59 (77.6)	1.17	1.02 – 1.36	1.03	0.88 – 1.21
Hormonal contraceptive use						
Never	40	16 (40.0)	1.00	ref	1.00	ref
Former	212	155 (73.1)	1.83	1.24 – 2.70	1.64	1.10 – 2.45

		hrHPV Antibody				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**AB+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Current	127	87 (68.5)	1.71	1.15 – 2.55	1.53	1.01 – 2.29
Smoking status						
Never	278	188 (67.6)	1.00	ref		
Former	81	56 (69.1)	1.02	0.87 – 1.21		
Current	19	14 (73.7)	1.09	0.82 – 1.44		
Lifetime number of male sex partners§						
0–4	130	72 (55.4)	1.00	ref	1.00	ref
5–11	119	79 (66.4)	1.20	0.98 – 1.46	1.08	0.88 – 1.33
12+	126	104 (82.5)	1.49	1.25 – 1.77	1.29	1.06 – 1.56
Male sex partners in past 6 months						
No partners	82	52 (63.4)	1.00	ref		
Non-new partners only	206	137 (66.5)	1.05	0.87 – 1.27		
≥1 new partner	84	62 (73.8)	1.16	0.95 – 1.43		

*Numbers might not add up to the total number of subjects due to missing data.

†Other race included: African American, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, women reporting more than one race, and women reporting “other” as race.

‡Non-HPV-related STD included: chlamydia, herpes, gonorrhea, HIV, and syphilis.

§This category represents approximate tertiles.

Table 4

Analysis of risk factors associated with seropositivity to multiple high-risk HPV types vs a single high-risk HPV type in mid-adult women (N=258).

		Seropositivity to multiple hrHPV types				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**Multiple AB+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Age (years)						
30–34	98	61 (62.2)	1.00	ref		
35–39	65	43 (66.2)	1.06	0.84 – 1.34		
40–44	50	36 (72.0)	1.16	0.92 – 1.46		
45–50	45	31 (68.9)	1.11	0.86 – 1.42		
Race						
White	201	133 (66.2)	1.00	ref	1.00	ref
Asian	26	13 (50.0)	0.76	0.51 – 1.12	0.81	0.53 – 1.24
Other†	31	25 (80.7)	1.22	1.00 – 1.49	1.15	0.94 – 1.40
Age at sexual debut (years)						
≤15	48	39 (81.3)	1.00	ref	1.00	ref
16–19	121	81 (66.9)	0.82	0.68 – 0.99	0.89	0.75 – 1.07
≥20	79	46 (58.2)	0.72	0.57 – 0.90	0.88	0.68 – 1.14
Marital status						
Single or separated	112	78 (69.6)	1.00	ref		
Married or living with a partner	145	93 (64.1)	0.92	0.77 – 1.09		
Number of pregnancies						
0	107	64 (59.8)	1.00	ref	1.00	ref
1–3	123	83 (67.5)	1.13	0.93 – 1.38	1.04	0.85 – 1.27
≥4	28	24 (85.7)	1.43	1.15 – 1.78	1.24	0.98 – 1.57
History of abnormal Pap test	120	83 (69.2)	1.08	0.91 – 1.29		
History of genital warts	30	23 (76.7)	1.18	0.95 – 1.47		
History of non-HPV-related STD‡	59	45 (76.3)	1.20	1.01 – 1.44	1.04	0.87 – 1.25
Hormonal contraceptive use						
Never	16	7 (43.8)	1.00	ref	1.00	ref
Former	155	110 (71.0)	1.62	0.92 – 2.86	1.22	0.69 – 2.16

		Seropositivity to multiple hrHPV types				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**Multiple AB+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Current	87	54 (62.1)	1.42	0.79 – 2.54	1.10	0.62 – 1.96
Smoking status						
Never	188	126 (67.0)	1.00	ref		
Former	56	36 64.3)	0.96	0.77 – 1.20		
Current	14	9 (64.3)	0.96	0.64 – 1.11		
Lifetime number of male sex partners§						
0–4	72	37 (51.4)	1.00	ref	1.00	ref
5–11	79	51 (64.6)	1.26	0.95 – 1.66	1.24	0.92 – 1.68
12+	104	81 (77.9)	1.52	1.18 – 1.94	1.33	0.98 – 1.80
Male sex partners in past 6 months						
No partner	52	30(57.7)	1.00	ref	1.00	ref
Sex with non-new partners only	137	90 (65.7)	1.14	0.88 – 1.48	1.06	0.82 – 1.38
≥1 new partner	62	46 (74.2)	1.29	0.98 – 1.69	1.18	0.90 – 1.56

*Numbers might not add up to the total number of subjects due to missing data.

†Other race included: African American, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, women reporting more than one race, and women reporting “other” as race.

‡Non-HPV-related STD included: chlamydia, herpes, gonorrhea, HIV, and syphilis.

§This category represents approximate tertiles.

Table 5

Analysis of risk factors associated with DNA positivity to any high-risk HPV type in mid-adult women (N=379).

		hrHPV DNA				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**DNA+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Age (years)						
30–34	138	29 (21.0)	1.00	ref	1.00	ref
35–39	91	13 (14.3)	0.68	0.37 – 1.24	0.76	0.39 – 1.50
40–44	73	9 (12.3)	0.59	0.29 – 1.17	0.62	0.33 – 1.17
45–50	77	6 (7.8)	0.37	0.16– 0.85	0.51	0.21 – 1.25
Race						
White	299	48 (16.1)	1.00	ref	1.00	ref
Asian	42	2 (4.8)	0.30	0.07 – 1.18	0.49	0.12 – 2.08
Other†	38	7 (18.4)	1.15	0.56 – 2.35	1.25	0.60 – 2.59
Age at Sexual debut (years)						
≤15	65	13 (20.0)	1.00	ref		
16–19	178	27 (15.2)	0.76	0.42 – 1.38		
≥20	120	17 (14.2)	0.71	0.37 – 1.37		
Marital status						
Single or separated	147	36 (24.5)	1.00	ref	1.00	ref
Married or living with a partner	231	21 (9.1)	0.37	0.23 – 0.61	0.50	0.30 – 0.82
Number of pregnancies						
0	149	33 (22.2)	1.00	ref	1.00	ref
1–3	184	19 (10.3)	0.47	0.28 – 0.79	0.56	0.32 – 0.98
≥4	46	5 (10.9)	0.49	0.20 – 1.19	0.58	0.23 – 1.45
History of abnormal Pap test	158	36 (22.8)	2.40	1.46 – 3.95	1.61	0.88 – 2.92
History of genital warts	42	5 (11.9)	0.77	0.33 – 1.82		
History of non-HPV-related STD‡	76	7 (9.2)	0.57	0.27 – 1.20		
Hormonal contraceptive use						
Never	40	4 (10.0)	1.00	ref		
Former	212	25 (11.8)	1.18	0.43 – 3.21		

		hrHPV DNA				
			Univariate Analysis		Multivariate Analysis	
Variables	**N***	**DNA+ (%)**	**RR**	**(95% CI)**	**RR**	**(95% CI)**
Current	127	28 (22.1)	2.20	0.82 – 5.91		
Smoking status						
Never	278	33 (11.9)	1.00	ref	1.00	ref
Former	81	17 (21.0)	1.77	1.04 – 3.01	1.57	0.95 – 2.60
Current	19	7 (36.8)	3.10	1.59 – 6.07	2.51	1.40 – 4.49
Lifetime number of male sex partners§						
0–4	130	9 (6.9)	1.00	ref	1.00	ref
5–11	119	17 (14.3)	2.06	0.96 – 4.46	1.71	0.79 – 3.70
12+	126	31 (24.6)	3.55	1.76 – 7.17	2.23	0.99 – 5.06
Male sex partners in past 6 months						
No partners	82	9 (11.0)	1.00	ref		
Non-new partners only	206	34 (16.5)	1.50	0.75 – 3.00		
≥1 new partner	84	14 (16.7)	1.52	0.70 – 3.32		

*Numbers might not add up to the total number of subjects due to missing data.

†Other race included: African American, American Indian/Alaska Native, Native Hawaiian/other Pacific Islander, women reporting more than one race, and women reporting “other” as race.

‡Non-HPV-related STD included: chlamydia, herpes, gonorrhea, HIV, and syphilis.

§This category represents approximate tertiles.